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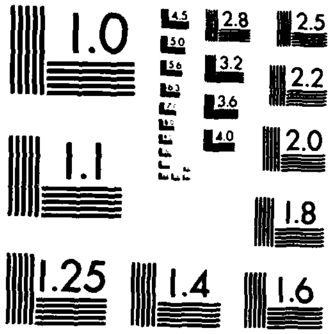

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DOSE LEVEL EFFECTS OF TRIAZOLAM ON SLEEP AND RESPONSE TO A SMOKE DETECTOR ALARM

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SUMMARY

Increasing attention is being given to the relative effects of hypnotic dose level on efficacy, sleep structure and next-day performance. This paper presents the results of .25 mg and .5 mg of triazolam on efficacy, sleep stages and awakening to a smoke detector when compared to each other and to subjects receiving a placebo.

METHOD

Subjects were 36 male poor sleepers (sleep-onset insomnia), mean age 20.1 ± 3.0 years, who received similar capsules of either placebo or triazolam at 21.00 h for five consecutive nights. Bed time was 22.00-05.00 h and sleep EEGs were recorded and scored according to usual procedures. On nights 1 and 4, a standard home smoke detector alarm was sounded during Stage 2, 5 min after sleep onset; in slow wave sleep (SWS); and at the time of the morning awakening. The alarm registered 78 dB SPL at the pillow. Reaction time (RT) to a button press was recorded. If the subjects did not respond after three, 1-min alarms were sounded, a "no response" was scored for that trial.

RESULTS

Sleep. Compared to placebo, both dose levels significantly reduced sleep latency, but they did not differ from each other. Other efficacy measures followed a similar pattern.

Compared to the placebo group, drug subjects had significantly more Stage 2, less SWS, and an increase in REM latency. Delta count was similar to SWS and spindle rate per minute (high to low) was .5 mg, .25 mg, and placebo. There were no consistent dose-level effects.

Smoke Detector. On the first smoke detector night, all placebo subjects awakened to each presentation of the alarm. For the hypnotic groups, two .25 mg subjects and one .5 mg subjects failed to awaken at the sleep-onset presentation. Six in both hypnotic groups (50%) failed to awaken during SWS. The RT for those who were awakened was consistently longer for the drug groups, but these differences were statistically

significant from placebo only during SWS. The respective SWS RT (secs) for .5 mg, .25 mg, and placebo subjects were 51 ± 52.1, 50 ± 55.2, and 13 ± 8.7. All subjects awoke to the morning presentation with similar RTs, <10 sec for the 3 groups.

Though the drug group showed some sensitization to the alarm or hypnotic tolerance on the second detector night, 3 subjects (2 in the .25 mg group and 1 in the .5 group) failed to awaken to Stage 2 alarm. Five subjects in the .25 mg group and 4 subjects in the .5 mg group failed to awaken during SWS. The EEG arousal and behavioral response latencies were shorter for those who were awakened, and response latencies were not significantly different from the placebo group.

CONCLUSION

In this sample of young adult poor sleepers, .25 mg was as effective as .5 mg of triazolam. The changes in sleep structure were less for the lower dose level. But both dose levels were similar in reducing the likelihood that subjects taking triazolam would awaken to a smoke detector during the first third of a night's sleep. By morning, all subjects were easily awakened by the detector. Similar patterns of arousal from sleep have been reported for other hypnotics.

INTRODUCTION

Increasing attention is being given to the relative effects of dose level on efficacy, sleep structure, and next-day performance. It was the conclusion of Johnson and Chernik (1982) that, in chronic use, dose level was more closely related to next-day performance than was half-life. While the effects of dose levels on efficacy and performance have been frequently examined, there are relatively fewer studies that have examined dose-level effects on sleep structure and even fewer studies of the dose-level effects on EEG activity. To our knowledge, there are no reports of dose-level effects on the arousal threshold and, more specifically, to the awakening to a smoke detector alarm. In this study, the effects of two dose levels of triazolam, .25 mg and .5 mg, on sleep structure and on the arousal response to a smoke detector alarm were examined.

When used over more than one night, benzodiazepines produce consistent changes in sleep structure, an increase in Stage 2, a decrease in slow wave sleep (SWS), and an increase in REM latency. A decrease in delta wave activity and an increase in sleep spindles are usually reported with benzodiazepine use. These changes have been sensitive to dose levels for a variety of benzodiazepines (Gaillard et al. 1973; Karacan et al. 1981; Bonnet et al. 1981; Roehrs et al. 1985; Nicholson and Stone 1982). Hirshkowitz et al. (1982) reported the most extensive study of the effect of varying dose levels of several types of drugs plus l-tryptophan and caffeine on sleep spindle activity. Of the 10 compounds evaluated, only the two benzodiazepines, flurazepam and WE-941, showed a spindle increase over baseline. For both benzodiazepines, the largest increase in spindles over baseline was seen at the higher dose levels. A similar extensive dose-level study has not been reported for EEG activity in the delta 1-4 c/sec range, though Karacan et al. (1981) reported a linear decrease in delta activity with increasing dose levels of flurazepam.

Sedative hypnotics reduce the number of nocturnal awakenings and also produce subjective reports of "deeper" sleep. Objective measures of arousal threshold (Bonnet et al. 1979; Johnson et al. 1979; Spinweber and Johnson 1982; Johnson and Spinweber 1983) have confirmed these subjective reports, but the effects of dose level on arousal threshold have not been reported.

METHODS

Subjects. Thirty-six male students from the Naval School of Health Sciences, mean age 20.1 ± 3.0 years, participated. On our Sleep Questionnaire, each subject stated he was a "poor" or "very poor" sleeper and took 45 min or longer to fall asleep, three to five times per week. Sleep-onset insomnia had been present for over six months for all subjects. There were no sleep complaints other than those associated with falling asleep. These subjects would be classified as meeting the diagnostic criteria for "disorders of initiating and maintaining sleep, psychophysiological, persistent" (DIMS) (Association of Sleep Disorders Center 1979).

Subjects were screened for possible psychiatric conditions, sensitivity to benzodiazepines, alcohol or drug abuse, and recent illnesses. All subjects were in good health and denied current or recent use of any type of sleep medication or other drugs.

All subjects were informed about the general nature of the experiment and signed Informed Consent and Privacy Act statements. They were asked to refrain from napping and taking drugs or alcohol during the course of the study. Breath analyzer and urine tests, used aperiodically, indicated no detectable use of alcohol or other drugs during the study.

Procedure. Each subject was randomly assigned to one of three groups in a double-blind, parallel-groups design with 12 subjects in each group. One hour before bedtime for five c nsecutive nights, Monday-Friday, subjects received similar capsules of either a placebo, or .25 mg or .5 mg triazolam. Bed time was 22.00-05.00 h.

Each subject slept in an electrically shielded, air conditioned room with soundproofing. All electrophysiological variables were recorded on an 8-channel Beckman dynograph. The electrooculogram (EOG) was recorded from biopotential electrodes placed on the outer canthus of each eye. The EEGs were obtained by use of silver chlorided disc electrodes from C_3 and O_1 electrode placements referenced to linked mastoids (A_1 + A_2). Both EOG and EEG time constants were 0.3 sec. Sleep stages for

all five sleep nights were determined according to standard criteria (Rechtschaffen and Kales 1968). EKG was recorded from electrodes placed on the right clavicle and on midline of 4th or 5th intercostal space.

Smoke Detector Arousals. On nights 1 and 4, three alarms from a standard home smoke detector were sounded. The smoke detector was enclosed in a box placed on a shelf beside the bed, slightly above pillow level, to bring the sound level to that usually experienced in the bed when the detector is located in a hall outside the bedroom. The sound level measured at the pillow was 78 dB SPL. The background noise varied from 32-34 dB SPL.

The alarm was activated by the technician who depressed a key on the computer terminal. It continued until the subject pushed a button to stop it or 60 sec had elapsed, when the computer would stop the alarm. If the subject made no response, the alarm was started again by depressing the key on the computer terminal. A total of three, 1-min alarms were presented before a "no response" was recorded. The time between the 1-min alarms was the time taken to depress the key on the computer terminal (a few seconds).

The schedule for arousals (nights 1 and 4) was:

1) First Stage 2: 5 min after sleep onset (the first well-defined K-complex or spindle).

2) First SWS: 20 min after the return to sleep following the first arousal. If the subject was not in SWS by 30 min following the return to sleep after the first arousal, he was aroused regardless of stage. In only two instances were subjects in Stage 2.

3) Morning wake-up at 05.00 h: If the subject was already awake, the response was not used. On night 1, eight subjects were awake before the alarm was sounded, three in the placebo group, one in the .25 mg group, and four in the .5 mg group; on night 4, no subject was awake.

There had to be no major body movement ($\geq$8 sec) for 10 min prior to an arousal

attempt except for the 0500 arousal. For arousals 1 and 2, the stage of sleep had to be well-defined for 5 min.

Three measures were obtained from each presentation: EEG arousal latency, behavioral response latency, and heart-rate response (see Figure 1). EEG arousal latency was the elapsed time (secs) between alarm onset and the appearance of fast EEG activity combined with muscle activity, usually followed by alpha activity. For those subjects who did not awaken, and thus did not push the button, the EEG was examined to see if any stage changes to a lighter stage of sleep had occurred. Such a response could be viewed as a partial arousal. Analysis of EEGs indicated there were no consistent differences between the groups in the occurrences of EEG shifts to lighter sleep stages.

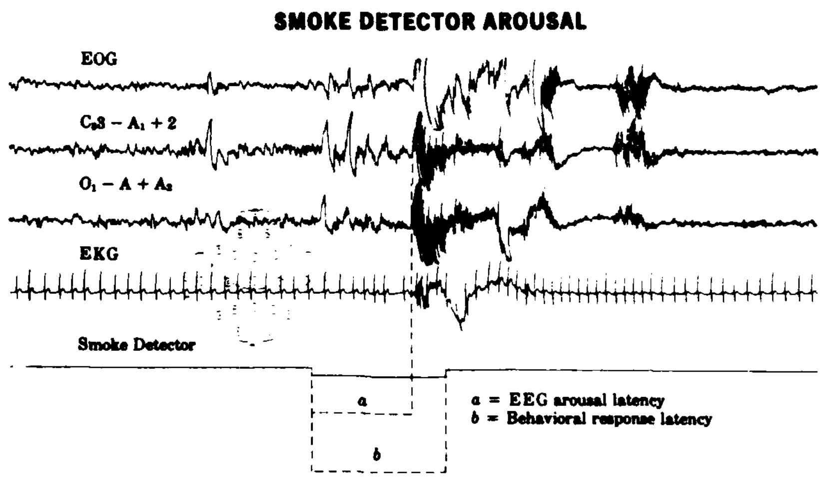

Figure 1. Illustration of EEG arousal latency and behavioral response latency to onset of smoke detector alarm.

Behavioral response latency was the elapsed time between the onset of the first smoke detector alarm and the subject's response. If the response occurred during the second or third 1-min presentation, the total elapsed time was recorded, e.g., 150 sec if the response occurred 30 sec after the onset of the third presentation. The

elapsed time between the EEG arousal and the behavioral response was also calculated. This difference reflects the time necessary for the subject to awaken to the point he can remember the instructions and make a button push response. The results of this analysis were similar to those for the total behavioral response latency.

The basal, or pre-alarm, heart rate was obtained by counting the heart beats in two movement-free, 10-sec intervals prior to detector onset and then averaged to obtain an average rate per min. The immediate phasic (orienting) accelerative response was seen at the onset of the detector alarm and, in some instances, at the offset. In most instances, the heart-rate acceleration was followed by deceleration during sleep, as has been previously noted (Johnson and Lubin 1967). Similar heart-rate response patterns were seen for all groups.

The increase in heart rate associated with the EEG arousal was used as the measure of heart-rate response. This measure was obtained by counting the number of beats in the 10 sec that followed the onset of the EEG arousal. This count was compared to the average of the two 10-sec periods prior to detector alarm onset. This difference, of course, includes the increase to the total arousal response and can be viewed as another indicator of the degree or level of arousal; i.e., a more aroused subject would have a higher heart-rate increase.

Sleep Measures. Sleep latency, sleep efficiency, percent Stage 2, percent SWS, percent REM, and REM latency were obtained. Sleep latency was the only measure not clearly influenced by arousal (nights 1 and 4) or performance (nights 2 and 5). On night 3, sleep was not interrupted. Since laboratory conditions were the same for all subjects, the influence of the research procedures should be similar for each group.

On-line EEG analysis. Detection of delta half-waves (0.5-2 c/sec) and sleep spindle bursts (11.75-15 c/sec) was accomplished on-line using the Smith phasic EEG detector (Smith et al. 1975). The recording and counting procedures and comparability of measures of spindle and delta activity, as obtained via use of the Smith on-line analysis and off-line computer analysis, were previously published in Johnson et al. (1979). Delta and spindle counts were obtained during the uninterrupted night of sleep, night 3.

Statistical Analysis. The sleep measures were analyzed by Analysis of Variance (ANOVA) for repeated measures using the Geisser and Greenhouse (1958) conservative P values from the BMDP2V program. The factors were groups, nights, and night-by-group interaction. When group F values were significant, a Hotelling T^2 test was used to evaluate the difference between groups over the five nights. Hotelling's T^2 makes possible the evaluation of between-groups differences with repeated measures and thus provided a test of profile level differences over the study period (Timm 1975). Between-groups differences for individual nights were evaluated by *t* tests for independent groups. The variability from night-to-night makes these *t* values less stable than the Hotelling T^2 results. EEG delta and spindle groups differences were evaluated by ANOVA and *t* tests were used for pairwise comparisons. Heart-rate changes and response latencies to the smoke detector alarm were examined by use of *t* tests for independent measures.

RESULTS

For nights, the F values were significant for all comparisons and will not be reported separately for each variable. There was only one significant interaction, the night-by-group interaction for SWS. This interaction was ordinal, therefore, not altering the straightforward interpretation of the main effects.

Hypnotic Efficacy

Sleep Latency. The main effect of groups was significant: $F(2,33) = 15.8$, $p<.001$. The data in Figure 2 reflect the consistency of the placebo vs. triazolam differences over each of the five nights. Between-groups comparisons indicated that placebo was significantly different from both drug groups. The T^2 values for the .5 mg and .25 mg groups vs. placebo group comparisons were 44.7, $p<.007$ and 27.6, $p<.008$, respectively. The T^2 value for the profile difference between the two dose levels was not significant. Night-by-night pairwise comparisons indicated the .25 mg group latency was significantly lower than the placebo group on three nights, while latency for the .5 mg group was significantly lower on all five nights. Latencies for the two dose levels did not differ significantly for any night.

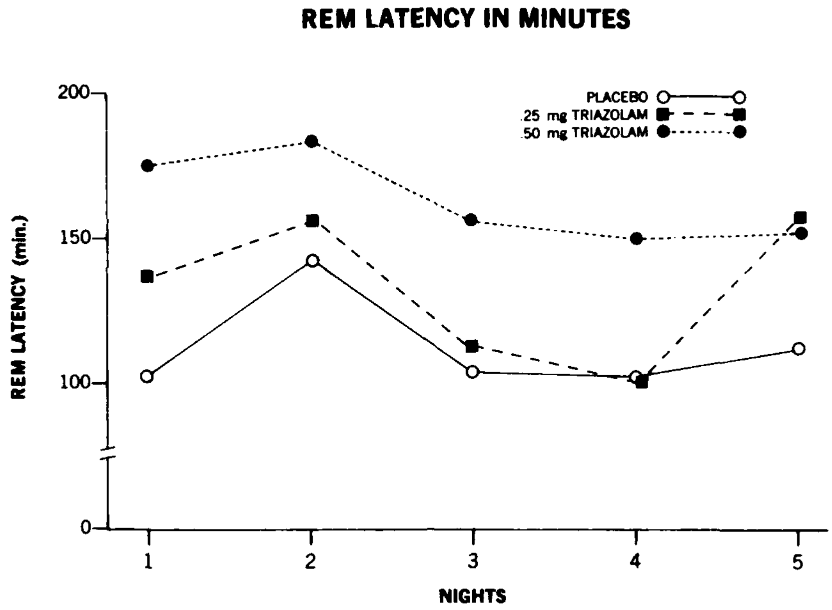

Figure 2. Sleep latency, to Stage 2 onset, for three groups for the five-night study.

Sleep Efficiency. This sleep index was artificially reduced by the awakenings for performance testing (nights 2 and 5) and by the response to smoke detector alarms (nights 1 and 4). The subjects who received triazolam had significantly higher sleep efficacy: $F(2,33) = 7.50$, $p<.0001$. Subjects who received triazolam returned to sleep faster after the awakenings than did the placebo subjects. Sleep efficiency for the two drug groups was not significantly different.

Sleep Stages

Stage 2 Percent. Compared to placebo subjects, there was a significant increase in Stage 2 in the triazolam subjects, $F(2,33) = 7.77$, $p<.002$ (Figure 3). Analysis of profile amplitude differences indicated that only the T^2 value for the .5 mg group vs. placebo group was significant, $T^2 = 25.8$, $p<.01$.

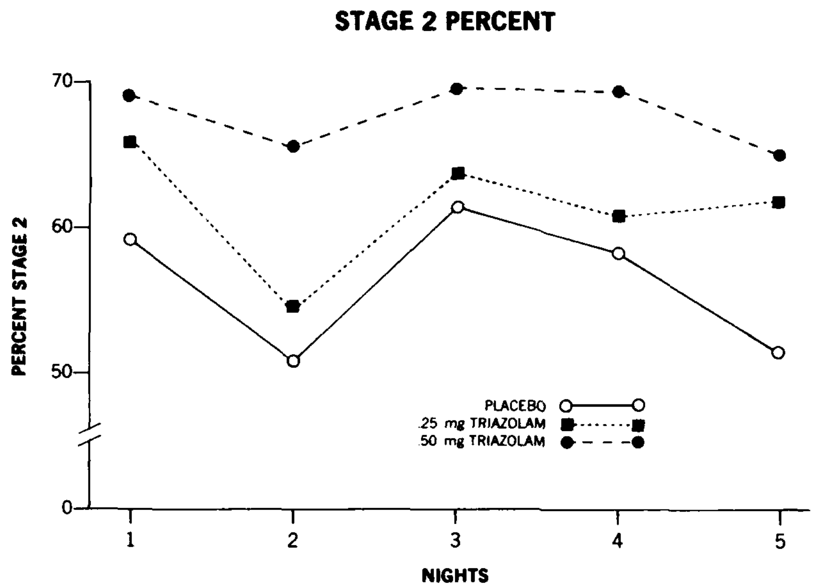

Figure 3. Stage 2 percent for the three groups for the five study nights.

On one of the five nights, Stage 2 percent was significantly higher in the .25 mg group than the placebo group. For the .5 mg group, Stage 2 was significantly higher than the placebo group on all nights and significantly higher than the .25 mg group on two nights.

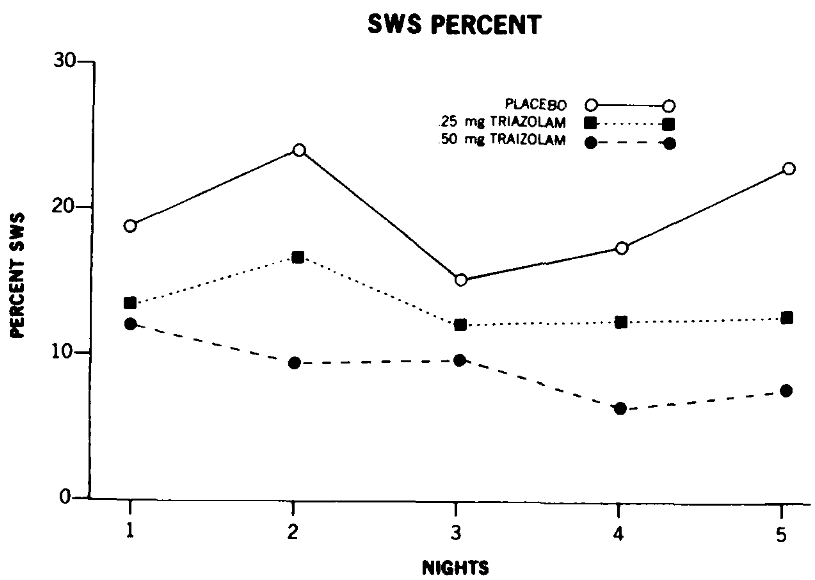

Figure 4. Slow Wave Sleep (Stages 3 and 4) percent for each group for the five study nights.

SWS. The data in Figure 4 also indicate a consistent pattern for SWS over the five nights. The group F value was $F(2.33) = 5.06$, $p<.01$. The T^2 comparisons revealed no significant between-group difference between the placebo and .25 mg groups. For the .5 mg group, SWS percent was significantly lower than the placebo group, $T^2 = 4.10$, $p<.0001$, and the .5 mg group had a significantly lower profile over the five nights than that for the .25 mg group, $T^2 = 19.6$, $p<.03$. However, when pairwise contrasts for individual nights were made, the two drug groups did not differ significantly on any night. Compared to the placebo group, the .25 mg dose group had significantly less SWS on one night, and the .5 mg group had significantly less SWS on three nights.

REM latency. REM latency was significantly longer for those receiving triazolam, $F(2,33) = 4.11$, $p<.025$. The latencies over the five nights are presented in Figure 5. Though the latency pattern was similar over the five nights, the between-group profile contrasts revealed no significant T^2 values. The .25 mg group REM latency did not significantly differ from placebo on any night, but the .5 mg group had a significantly longer latency on three nights. The two drug groups differed significantly on nights 3 and 4. One subject in the placebo group had sleep-onset REM. His latency to REM was 15 min from lights out and 4.5 min from Stage 1.

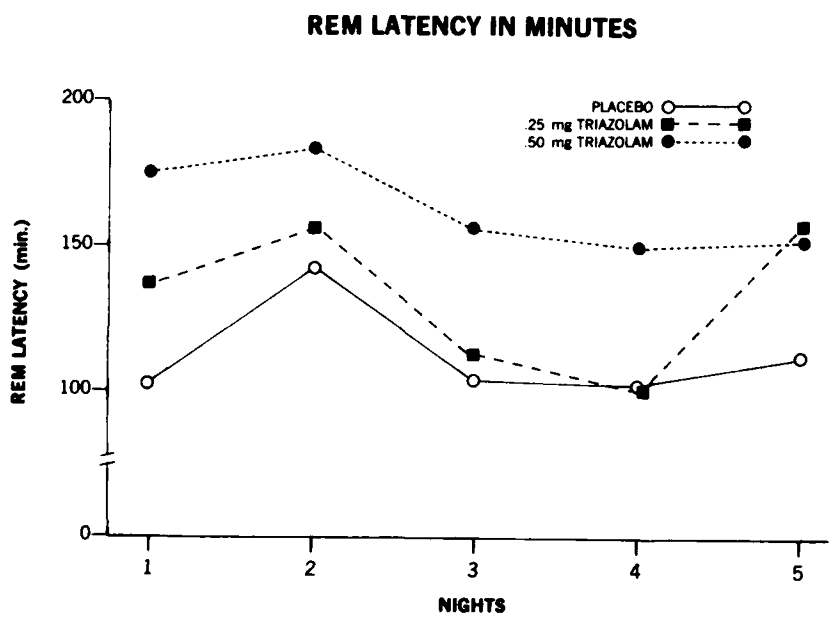

Figure 5. Latency (mins) to first REM period for three groups for each study night.

In contrast to the significant effect of triazolam over the treatment period on REM latency was the absence of any effect on REM percent. REM-NREM cycle length was not measured on each night, but on night 3, the uninterrupted sleep night, the respective REM-NREM cycle lengths were 92, 96, and 97 min for the placebo, .25 mg, and .5 mg groups, respectively.

Delta and Spindle Counts. The results for NREM delta and spindle counts per min for the uninterrupted night 3 sleep are presented in Table 1. While these means are lower than those for our previous studies, when subjects were screened for presence of SWS, these data are consistent with the results reported by Karacan et al. (1981), especially for delta. They used a similar spindle and delta analyzer in a young adult (mean age 24.9 years) sample of insomniacs. Though the increases in spindle bursts per min in the two hypnotic groups were in the expected direction, the differences were not statistically significant from the placebo group. There was a significant group difference for delta count and both drug groups' mean values were significantly lower than placebo ($t(22) = 3.24$, $p<.004$) for .5 mg vs. placebo and for .25 mg vs. placebo ($t(22) = 2.14$, $p<.04$). There were no significant differences between the two drug groups.

Table 1. EEG Detector Count for NREM Sleep

	GROUP		
	Placebo	.25 mg	.5 mg
	$\bar{X} \pm SD$	$\bar{X} \pm SD$	$\bar{X} \pm SD$
Spindle/min*	1.4(1.3)	2.4(1.6)	2.7(1.9)
Delta/min**	9.5(6.7)	4.6(4.3)	2.7(2.7)

* $F(2,33) = 2.22$, $p<.1241$

** $F(2,33) = 6.21$, $p<.0051$

Smoke Detector Response

Awakenings. The sedative hypnotic clearly increased the arousal threshold. On the first alarm night, 50% of the subjects receiving triazolam did not awaken during the three, 1-min alarms presented during SWS. Four subjects did not awaken when the detector alarm was sounded 5 min after sleep onset on night 1. The 05.00 h alarm easily awakened all subjects. All placebo subjects were awakened by all the alarms.

On the second arousal night, night 4, the pattern of arousals was the same, but slightly fewer triazolam subjects slept through the alarms. Nine subjects instead of twelve in SWS and three instead of four in Stage 2 sleep were not awakened during the first arousal. Again, all subjects were awakened at 05.00 h. Of the 12 subjects who did not awaken during SWS on night 1, eight (67%) did not awaken on night 4. Two of the four subjects who did not awaken to the alarm during early Stage 2 also failed to awaken on the fourth night. On both nights, subjects who did not awaken to the first arousal did not awaken during SWS.

EEG Arousal Latency. For those subjects who were awakened by the smoke detector, there were no group differences in the latency to the EEG arousal.

Behavioral Response Latencies. The latency from alarm onset to the behavioral response that turned off the alarm was longer for the .5 mg triazolam subjects for all three arousals on the first arousal night (see Figure 6). The .25 mg group was similar to the placebo group on the sleep-onset and morning arousals, but was similar to the .5 mg group during SWS. The placebo-drug group differences, however, were significant only during the SWS arousal ($t(16) = 2.33$, $p<.05$ for .25 mg and $t(16) = 2.26$, $p<.05$ for .5 mg). There were no significant drug group differences. Larger standard deviations for the drug groups reflected the greater intersubject variability in response latency. For example, during SWS on night 1, the SDs for placebo, .25 mg, and .5 mg were 8.7, 55.2, and 52.2 sec, respectively.

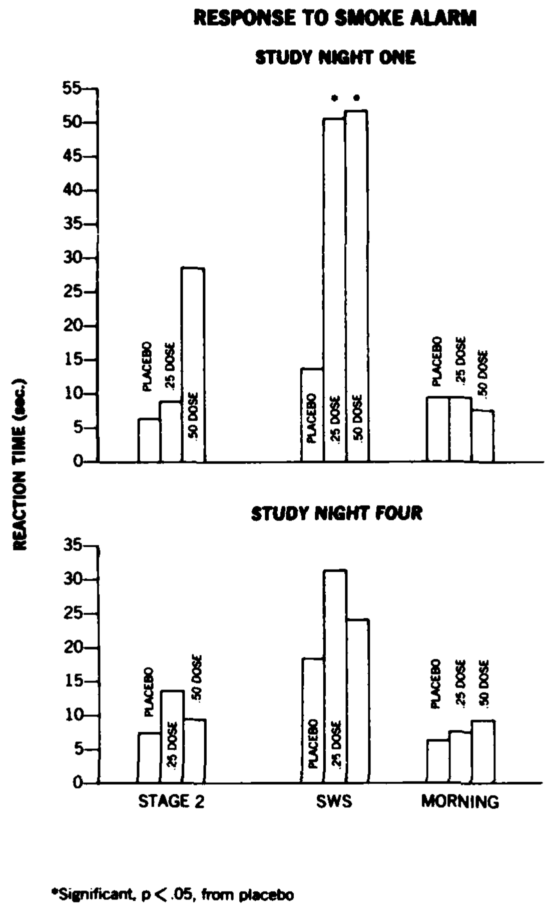

Figure 6. Reaction time (secs) from detector onset to button press for each group for the three arousals, study night 1 and study night 4.

On study night 4, the mean reaction times for the two hypnotic groups were generally faster than on night 1, and there were no significant group differences.

<u>Heart-Rate Response</u>. In all instances, when the heart rate during the 10-sec period after EEG arousal onset was compared to the basal heart rate, there was an increase in rate. An average increase of four beats was found between the baseline and arousal periods. There were no significant group differences for any arousal on either arousal night.

DISCUSSION

The unique contribution of this study was demonstrating the effect of the two dose levels of triazolam on response to a smoke detector alarm. The sedative effects of both doses were similar. The sedative effect was most pronounced on the first study night, particularly during the first part of the night. Not only did 50% of those receiving the hypnotic fail to awaken to three 60-sec, 78 dB SPL alarms when they occurred during the first SWS period about two hours after drug intake, but those who did respond were markedly slower in their response than the placebo subjects. The slower response was clearly seen on the first arousal shortly after the first Stage 2 onset in those receiving .5 mg.

Speed of response has been found to be most affected by hypnotics (Johnson and Chernik 1982; Wittenborn 1979). That observation was supported by our results. For those responding, there were no group differences in EEG arousal latencies, but a clear difference was seen in how long it took the hypnotic subject to make the response. Our results indicate that even though some subjects who take a hypnotic may awaken as quickly as those taking a placebo, their cognitive and motor responses after awakening will generally be slower.

By the fourth night of use, there was a marked reduction in the drug effect for both EEG arousal and behavioral response latencies. On night 4, the drug-group response times were not significantly different from placebo. However, nine (37.5%) of the subjects still did not awaken to the alarm during SWS, though this response was less than the 50% failure to awaken on night 1. This alteration may have been due to sensitization to the alarm or to tolerance of the sedative effects of the hypnotic or, possibly, to both mechanisms. Two-thirds of those who did not awaken during SWS on night 1 also did not awaken on night 4, indicating that some subjects may show a persistent sensitivity to the sedative effects of the hypnotic.

The implications of these findings are of importance for fire safety or response to any auditory emergency signal, and the reader should not assume that these increases in arousal level are present only for those taking triazolam. Bonnet et al. (1979) have found a similar pattern of increased arousal threshold for flurazepam and pentobarbital, and Johnson et al. (1979) found the same increase in arousal threshold for

flurazepam as that reported by Bonnet et al. (1979). Those who take any sedative hypnotics, thus, should be informed of the increase in arousal threshold and of their probable slower reaction time after awakening.

In this sample of young adult, sleep-onset insomniacs, the .25 mg dose was as effective as the .5 mg dose in reducing sleep latency. Other studies have found .25 mg to be a clinically-effective dose (Roth et al. 1977; Nicholson et al. 1982). In a recent report, Roehrs et al. (1985) not only found .25 mg to be as effective as .5 mg but also reported no rebound insomnia in those patients receiving .25 mg. Though the mean values for the .5 mg and .25 mg groups seldom differed significantly from each other when the pattern over the five nights was examined, the .5 mg subjects consistently had more Stage 2 sleep, less SWS, and longer REM latency. There were also fewer delta waves for the .5 mg subjects. Though nonsignificant, spindle rate followed the expected larger increase in the higher dose group. But the low spindle rate/min for all groups in this study was not consistent with other reports which have shown higher resting spindle rates and larger benzodiazepine-related spindle increases. The records with the lowest rates were reanalyzed with similar results. Visual analysis of the records confirmed the low spindle activity, indicating that not only was the detector giving reliable results, but the count appeared consistent with visual analysis. In our previous studies, we have included only subjects with greater than 5% SWS. Six of the 36 subjects in this study had less than 5% SWS on their first night, but we know of no consistent relationship between percent SWS and spindle activity.

The sleep-stage changes were consistent with those generally reported in the literature, and while the .5 mg dose produced a larger decrease in SWS, more Stage 2, and a longer REM latency. These differences were nonsignificant. In this study, the effect of triazolam on REM sleep was clearly specific to latency. For those receiving triazolam, once REM sleep appeared, the REM-NREM cycle length was similar to placebo, and the duration of the REM periods was of sufficient length to maintain REM percent comparable to that of subjects receiving the placebo. Similar to the benzodiazepine-induced EEG delta and spindle changes, there are no clear neurophysiological or neurochemical explanations for the benzodiazepine-related delay in REM latency. Also, as is true for the EEG changes, there are no significant behavioral or therapeutic correlates of delayed REM onset.

The lack of any difference in the heart-rate response was consistent with the EEG arousal data. The hypnotic appeared to have no differential effect on the autonomic nervous system response. In previous studies (Muzet et al. 1982; Gaillard et al. 1973), an increase in heart rate has been reported during benzodiazepine use. While there was a drug-related increase in heart rate in this study and a dose-level effect was suggested, the large interindividual variability prevented the placebo-drug group differences from being statistically significant.

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Thirty-six young adult, male subjects with sleep-onset insomnia were equally divided into placebo, .25 mg and .50 mg triazolam groups to examine the effects of the hypnotic, with particular attention to dose level, on efficacy, sleep stages, and awakening to a smoke detector alarm. On nights 1 and 4 of a five-consecutive night protocol, a standard home smoke detector alarm was sounded during Stage 2, 5 minutes after sleep onset, in slow wave sleep (SWS), and at the time of the early morning awakening. The alarm registered 78 dB at

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the pillow. EEG arousal latency and reaction time to a button press were studied. Failure to awaken to three one-minute alarm presentations was scored as no response. Both dose levels produced similar reduction in sleep latency, decrease in SWS, increase in Stage 2, and increase in sleep latency. Both dose levels showed a similar sedative effect to the smoke alarm. Fifty percent failed to awaken on night 1 during SWS, and EEG arousal and response latencies were significantly slowed. Some tolerance was seen by night 4. By morning, all subjects were easily awakened on both nights. The .25 mg dose is clearly an effective dose level for both sleep efficacy and sedative effects to outside noise. The sedative effects, in some instances, could pose a potential problem.

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